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Relapse of endometrial hyperplasia after conservative treatment: a cohort study with long-term follow-up

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STUDY QUESTION: What is the risk of relapse for women with endometrial hyperplasia treated with levonorgestrel-releasing intrauterine system (LNG-IUS) or oral progestogens?

SUMMARY ANSWER: Relapse of complex endometrial hyperplasia after initial regression occurs often and it occurs less often in women treated with LNG-IUS than with oral progestogens.

WHAT IS KNOWN ALREADY: The LNG-IUS and oral progestogens are used to treat women with endometrial hyperplasia and achieve regression. There is uncertainty over whether further surveillance for these women is necessary as the risk for relapse is unknown.

STUDY DESIGN, SIZE, DURATION: A cohort study of 219 women with complex non-atypical or atypical endometrial hyperplasia who were treated and achieved initial regression with LNG-IUS ($n = 153$) or oral progestogens ($n = 66$) from August 1998 until December 2007 and followed up for >5 years. The mean length of follow-up was 74.7 ± SD 31.8 months for the LNG-IUS versus 87.6 ± SD 42.2 months for the oral progestogen group.

PARTICIPANTS/MATERIALS, SETTING, METHODS: We evaluated the proportion of women who relapsed or had hysterectomy after initial regression with LNG-IUS compared with oral progestogens by logistic regression and adjusting for confounding. The time from regression to relapse was explored through a survival analysis.

MAIN RESULTS AND THE ROLE OF CHANCE: Relapse of hyperplasia occurred in 13.7% (21/153) of women treated with LNG-IUS compared with 30.3% (20/66) of women treated with oral progestogens [adjusted odds ratio (OR) = 0.34, 95% confidence interval (CI): 0.17–0.7, $P = 0.005$]. Relapse rates over long-term follow-up were lower for complex non-atypical hyperplasia compared with atypical hyperplasia for both LNG-IUS (12.7%, 18/142 versus 27.3%, 3/11, respectively; $P \leq 0.001$) and oral progestogens (28.3%, 17/60 versus 50%, 3/6, respectively; $P \leq 0.001$). The survival analysis indicates that relapse occurred less often with LNG-IUS at 12, 24, 36, 48, 60 and >60 months of follow-up (hazard ratio 0.37, 95% CI: 0.2–0.7, $P = 0.0013$). There were no events of relapse after 48 months from regression with oral progestogens, but 5 women treated with LNG-IUS relapsed after 60 months when treatment was discontinued. Hysterectomy rates were lower in the LNG-IUS than oral progestogen group during follow-up (19.6%, 30/153 versus 31.8%, 21/66, respectively, OR = 0.52, 95% CI: 0.27–1, $P = 0.05$). Endometrial cancer was diagnosed in 2 (11.8%) women who had hysterectomy ($n = 17$) because of relapse.

LIMITATIONS, REASONS FOR CAUTION: We are unable to accurately estimate the cancer risk in women who relapse during follow-up as only 17 out of 41 who relapsed underwent hysterectomy.

WIDER IMPLICATIONS OF THE FINDINGS: Relapse of endometrial hyperplasia after initial regression occurs often and long-term follow-up is advised.

STUDY FUNDING/COMPETING INTEREST(S): Ioannis D. Gallos and this study were funded through a grant from Wellbeing of Women (ELS022). No competing interests.

Key words: relapse / endometrial hyperplasia / levonorgestrel-releasing intrauterine system / oral progestogens / prospective cohort

Introduction

Endometrial hyperplasia (EH) is the precursor of endometrial carcinoma and it can progress to cancer if left untreated (Kurman et al., 1985). The World Health Organization (WHO) classification categorizes EH as simple (SH), complex (CH), simple atypical (SAH), or atypical complex (ACH) on the basis of architectural crowding and nuclear atypia (Tavassoli, 2003). The term atypical hyperplasia (AH) often encompasses ACH or SAH, because SAH is so rare. SH is often considered a variation of normal endometrium and its risk of progression to cancer is comparable to the normal population (<1%) (Kurman et al., 1985). CH has an intermediate risk of progression to cancer (~3%) and can be treated with hormone therapies (Kurman et al., 1985). The WHO classification can be confusing and a simpler classification of SH, CH and ACH has been proposed (Kurman et al., 1985). A meta-analysis found that the levonorgestrel-releasing intrauterine system (LNG-IUS) achieves regression in up to 92% of women (Gallos et al., 2010) and that the regression with LNG-IUS is higher than that with oral progestogens and reduces the number of hysterectomies performed for this condition. The mainstay treatment for ACH is hysterectomy because of the high risk of progression to cancer (up to 29%) and the possibility of concomitant cancer (up to 43%) in women undergoing hysterectomy (Kurman et al., 1985; Trimble et al., 2006). Hormonal therapies have also been used to treat ACH in young women who wish to preserve their fertility and it may be the only option for women with severe co-morbidities (Gallos et al., 2012).

Despite the initial regression of EH with hormonal therapies, caution has been advised because of the possibility of relapse (Gallos et al., 2012). In a meta-analysis for young women with ACH treated with hormones the summary estimate of the relapse rate was ~26% (Gallos et al., 2012). Considering that the majority of the studies in the literature have short durations of follow-up, the risk of relapse of ACH following an initial regression may even be higher. On the other hand, the majority of clinicians treat women with CH with hormonal therapies, but the risk of relapse for these women remains unknown (Gallos et al., 2011). This prevents many clinicians from embarking on long-term follow-up. Even though it is known from a case–control study that women diagnosed with CH are at higher risk of progression to cancer than healthy women (Lacey et al., 2010), the risk of relapse and a strategy for following up these women remains to be defined. In this study, we have conducted a cohort study with >5 years of follow-up for defining the relapse risk for women with CH and ACH treated with LNG-IUS or oral progestogens.

Materials and Methods

This was a comparative observational study. We recruited all women diagnosed with CH or ACH who underwent treatment with LNG-IUS or oral progestogens from August 1998 until December 2007 in a tertiary referral Hospital in Birmingham, UK. Recruitment for women treated with LNG-IUS was prospective and started from August 1998. For women treated with oral progestogens prospective recruitment started after December 2007. Women with CH and ACH treated with oral progestogens from August 1998 until December 2007 were invited for long-term follow-up in our clinic and they have continued to be followed since then. These women were identified through a central electronic histopathology database, which includes all patients diagnosed with EH in our hospital with no missing patients. The histopathological diagnoses were undertaken by two experienced gynaecological pathologists working independently; referral to the other pathologist for a second opinion was made in cases where there was diagnostic doubt, and a mutual consensus was then achieved. Women were reviewed in our gynecology outpatient clinic following diagnosis and were offered LNG-IUS (Mirena®, Bayer Schering Pharma AG, Berlin, Germany), oral progestogens or hysterectomy as part of our routine clinical practice. Women diagnosed with ACH were counseled and offered a hysterectomy. Women who declined surgery or who were medically unfit to undergo surgery were offered LNG-IUS or oral progestogens. The duration of oral progestogen treatment was ~6 months for most women (71.2%, 47/66) and varied from 3 months (24.2%, 16/66) up to 12 months (4.6%, 3/66) according to clinician preference. Further oral progestogens were then not continued. The LNG-IUS treatment was intended for 5 years. Study participants underwent regular review and endometrial histological surveillance by office endometrial sampling. Following LNG-IUS insertion or commencement of oral progestogen treatment, histological surveillance was performed on a six-monthly basis for the first 2 years to ensure regression occurred. Following the initial regression, women were followed yearly thereafter for 5 years to ascertain if relapse occurred and then the patients were given a choice to have continued yearly surveillance. Women who did not adhere to this strategy were invited for office review in order to obtain a longer than 5-year follow-up outcome. Ethical approval from the Coventry and Warwickshire Research and Ethics Committee was obtained for this study (LREC 09/H1211/30) to collect and analyze prospectively collected linked data without written consent.

The primary outcome for this study was to determine the proportion of women with CH or ACH who had a relapse of EH or cancer after showing histological regression following treatment with LNG-IUS compared with oral progestogens. We aimed to minimize the losses to follow-up and to achieve this we involved clinicians in primary care for contacting women and making arrangements for further surveillance. For this assessment, the results of follow-up histological examinations following the initial regression were classified as (i) *complete regression*—atrophy of glands, edematous fibrotic stroma or pseudodecidualization, with no evidence of hyperplasia. (ii) *Relapse*—failure to remain in regression with the evidence of CH, ACH or carcinoma. The secondary outcomes we studied were the hysterectomy rate for each treatment, the time interval from regression to relapse and the proportion of patients in both groups diagnosed with endometrial cancer during the follow-up. All outcomes were evaluated on an intention-to-treat basis.

The baseline characteristics and outcomes for the oral progestogen and LNG-IUS groups were analyzed using Mann–Whitney *U*-tests for non-parametric data and Pearson's chi-square tests (χ^2) for categorical data. For variables with a Gaussian distribution we report means and SD and for skewed data medians and interquartile ranges (IQR). Analysis of outcomes between the two treatment groups was performed by logistic regression to compute odds ratios (ORs) with their 95% confidence intervals (CI), adjusting for potential confounding factors. We adjusted for correlated confounding factors ($P < 0.1$) with both treatment modality and outcome and these were incorporated into the final model (Hosmer and Lemeshow, 2000). We constructed our survival analysis using the Cox proportional hazards model as it accounts for variable duration of follow-up, censoring of subjects, proportionality of event occurrence and time-to-event (Lin and Wei, 1989). To convert the results of the Cox model into absolute risk estimates, we calculated survival within our population using Kaplan–Meier estimates (Cox, 1972; Klein and Moeschberger, 2003). Missing data were handled by complete case analysis for our exposure (treatment modality) and outcomes (regression and hysterectomy)

and by multiple imputation for confounding variables (Rubin, 1972; Schafer, 1997). All analyzes were performed using STATA Version 12.1 (Release January 2012, STATA Corporation). A value of $P < 0.05$ was considered significant.

Results

During the study period, 527 women were diagnosed with CH or ACH and 260 were treated with progestogens (Fig. 1). We have excluded women who failed to achieve regression after progestogen treatment ($n = 24$). We have also excluded women who did not accept long-term follow-up following their initial regression ($n = 18$) or opted for hysterectomy ($n = 4$). As a result, we have included 219 women in our study from which, 66 were treated with oral progestogens and 153 with LNG-IUS. Table I shows the baseline characteristics of the women according to the type of treatment. Women treated with LNG-IUS were older and more likely to be menopausal. The mean follow-up was 74.7 ± SD 31.8 months for the LNG-IUS group and 87.6 ± SD 42.2 months for the oral progestogen group.

The relapse rate following regression with LNG-IUS treatment was 13.7% (21/153) and it was higher for ACH (27.3%, 3/11) than for CH (12.7%, 18/142). The relapse rate following regression with oral progestogens was 30.3% (20/66) and similarly it was higher for ACH (50%, 3/6) than for CH (28.3%, 17/60). The difference in relapse rates was significant between LNG-IUS and oral progestogens ($P = 0.004$) and this was confirmed when adjusted for menopause (adjusted OR = 0.34, 95% CI: 0.17–0.7, Table II). As a result, there were fewer hysterectomies performed with LNG-IUS treatment (19.6%, 30/153) compared with oral progestogens (31.8%, 21/66, $P = 0.05$). Overall, 41 women relapsed during follow-up and were offered hysterectomy. Only 17 women underwent hysterectomy and two were diagnosed with endometrial cancer (11.8%). One woman initially diagnosed with CH and treated with LNG-IUS progressed to endometrioid cancer with concomitant granulosa cell tumor of the ovary after 36 months from initial regression. Another woman initially diagnosed with ACH and treated with oral progestogens progressed to Stage Ia endometrioid cancer 6 months after initial regression.

The survival analysis in Fig. 2 indicates that relapse occurs less frequently after initial regression with LNG-IUS treatment than with oral progestogens over the 5-year follow-up (hazard ratio = 0.37, 95% CI: 0.2–0.7, $P = 0.0013$). Relapse also occurs sooner with oral progestogens. Relapse occurred at a median time of 32.2 months ± IQR 11.3–57.7 months following LNG-IUS treatment compared with 13.7 ± IQR 5.7–20.6 months following oral progestogens. No relapse was observed after 48 months from initial regression with oral progestogens compared with LNG-IUS, where 5 women relapsed after the 5-year period when this treatment was discontinued.

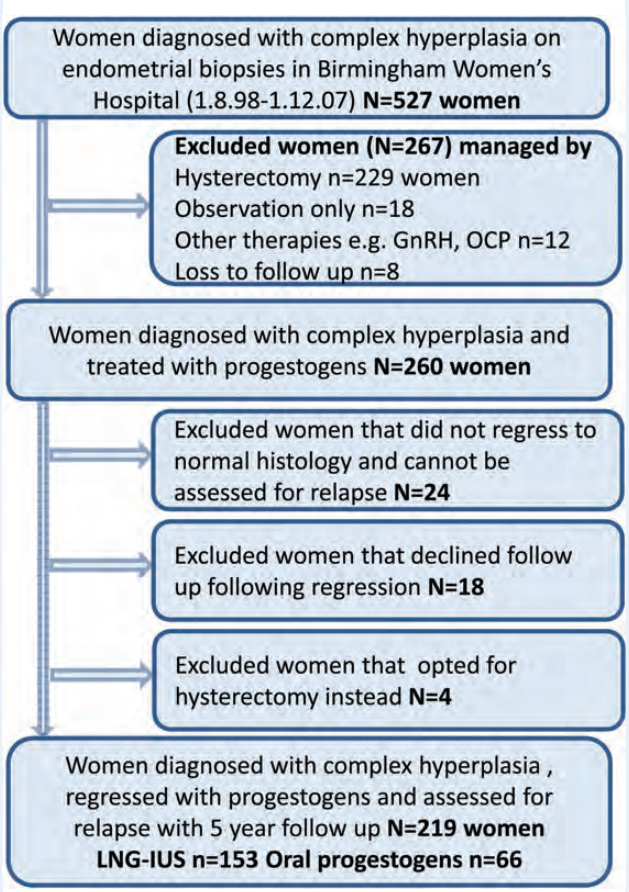


Figure 1 Schematic representation of patients included in the study analysis. OCP, oral contraceptive pill.

Discussion

The management of EH with progestogens is aimed to induce endometrial regression and prevent women from undergoing hysterectomy. This may be particularly appealing to young women wishing to preserve their fertility or women with multiple comorbidities who are poor surgical candidates. However, the relapse of ACH or CH following treatment with progestogens is common. The risk is higher when women are treated with oral progestogens compared with LNG-IUS and results in more hysterectomies. This study is unique in the literature as it follows-up women for >5 years and covers the period from their initial regression following progestogen treatment to the time of relapse. Our data suggest that this risk is high and discontinuing follow-up after an initial regression is not justified. Women treated with oral progestogens relapse earlier and no further events were recorded after 48 months from the initial regression. Women treated with LNG-IUS may relapse after 5 years when the LNG-IUS treatment is stopped and therefore we propose that if a replacement LNG-IUS is not carried out then these patients should be followed up for at least a further year. Women who relapsed during the follow-up were diagnosed with endometrial cancer in up to 12% of cases.

The design of our study and the long-term follow-up provide valuable information about the risk of relapse and aids the follow-up strategy for these women. We minimized missing data for the women treated with oral progestogens before August 2008 by recalling them for long-term surveillance. We achieved a high percentage of follow-up for relapse rate at 12, 24, 36, 48 and 60 months and we reduced potential follow-up bias. From our intended sample size we achieved a 98% follow-up for the relapse rate at 12 months, 94% for 24 months, 88% for 36 months, 79% for 48 months and 73% for 60 months. We also measured and adjusted for a large number

Table I Baseline characteristics of patients with endometrial hyperplasia who regressed with LNG-IUS or oral progestogens and were assessed for relapse.

	LNG-IUS (n = 153) n (%)	Oral progestogens (n = 66) n (%)	P-value
Age (years)	Mean 53 ± SD 10.1	Mean 50.4 ± SD 11.5	0.091
Parity	Mean 2.2 ± SD 1.4	Mean 2 ± SD 2.2	0.533
BMI (kg/m^2)	Mean 33.3 ± SD 10.2	Mean 32.5 ± SD 9	0.629
Endometrial thickness on ultrasound (mm) for menopausal women	Mean 10.2 ± SD 6.1	Mean 11.2 ± SD 7.7	0.377
Ethnic group			
Caucasian	116 (75.7)	49 (74.3)	
Asian	19 (12.5)	9 (13.6)	
Other	10 (6.6)	7 (10.6)	
Unknown	8 (5.2)	1 (1.5)	0.75
Menopausal status			
Premenopausal	75 (49)	46 (69.7)	
Post-menopausal	78 (51)	20 (30.3)	0.005
Hypertensive	58 (37.9)	19 (28.8)	0.195
Diabetic	23 (15)	9 (13.6)	0.788
HRT/tamoxifen use in last 5 years			
None	121 (79.1)	56 (84.9)	
HRT	30 (19.6)	8 (12.1)	
Tamoxifen	2 (1.3)	2 (3)	0.36
Endometrial histology			
Atypical hyperplasia	11 (7.2)	6 (9.1)	
Complex hyperplasia	142 (92.8)	60 (90.9)	0.629

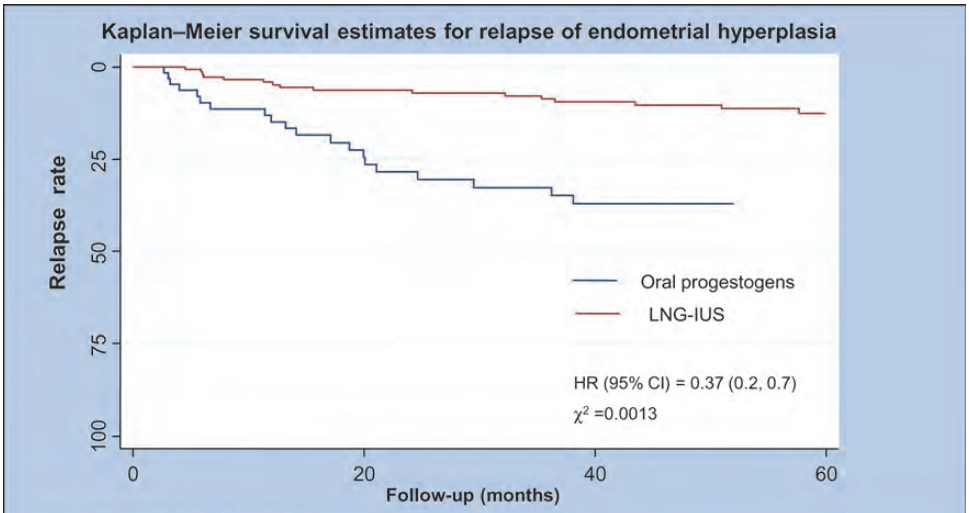
Table II Outcomes of patients assessed for relapse following initial regression after treatment with LNG-IUS or oral progestogens.

	LNG-IUS (n = 153) n (%)	Oral progestogens (n = 66) n (%)	P-value	OR (95% CI)	Adjusted OR (95% CI)
Time from diagnosis to last histological follow-up (months)	Mean 74.7 ± SD 31.8	Mean 87.6 ± SD 42.2	0.066		
Relapse of hyperplasia	21/153 (13.7)	20/66 (30.3)	0.005	0.37 (0.18–0.73)	0.34 (0.17–0.7)
Complex hyperplasia	18/142 (12.7)	17/60 (28.3)			
Atypical hyperplasia	3/11 (27.3)	3/6 (50)			
Hysterectomy performed	30/153 (19.6)	21/66 (31.8)	0.05	0.52 (0.27–1)	0.49 (0.25–0.97)
Cancer diagnosed	1/153 (0.65)	1/65 (1.5)	0.539		

CI, confidence interval.

of potential confounding factors. However, the observational design cannot exclude residual confounding from unmeasured variables, such as the change of weight during the follow-up or new onset of diabetes. We were also unable to accurately estimate the risk of cancer in women who relapse during the follow-up as only 17 out of 41 underwent hysterectomy.

The LNG-IUS is the treatment of choice for ACH and CH but oral progestogens remain popular among clinicians (Gallos *et al.*, 2011). It has been accepted practice to treat until an endometrial regression is confirmed histologically but, following this confirmation, there was uncertainty over whether women warrant further follow-up. The literature is scarce on the optimum follow-up strategy and guidelines



Cumulative event rates of relapse by fixed time points

Therapy	12 months n relap./t (%)	24 months n relap./t (%)	36 months n relap./t (%)	48 months n relap./t (%)	60 months n relap./t (%)	>60 months n relap./t (%)
LNG-IUS	6/153 (3.9)	9/153 (5.9)	12/153 (7.8)	14/153 (9.2)	16/153 (10.4)	21/153 (13.7)
Oral progestogens	9/66 (13.6)	16/66 (24.2)	18/66 (27.3)	20/66 (30.3)	20/66 (30.3)	20/66 (30.3)
Total	15/219 (6.8)	25/219 (11.4)	30/219 (13.7)	34/219 (15.5)	36/219 (16.4)	41/219 (18.7)

Figure 2 Kaplan–Meier survival curves for all events of endometrial hyperplasia relapse in women who initially regressed after treatment with LNG-IUS or oral progestogens. CI, confidence interval; HR, hazard ratio.

are lacking. Previous studies have concentrated mostly on the time taken for women with ACH or CH to regress to normal endometrium (Orbo *et al.*, 2008; Varma *et al.*, 2008). Two small studies did not report any diagnoses of endometrial cancer during follow-up but did not specifically report on the risk of relapse during follow-up (Orbo *et al.*, 2008; Buttini *et al.*, 2009). However, a case–control study found that women with a previous diagnosis of ACH or CH were at higher risk of developing endometrial carcinoma over the long term, which may be up to 21 times higher than the average population risk (Lacey *et al.*, 2010). This higher risk of cancer diagnosis for women previously diagnosed with EH may be justified from the high risk of relapse of EH following initial treatment.

The difference in relapse rates of LNG-IUS over oral progestogens for the treatment of EH found in our study can be explained by the duration of treatment. The LNG-IUS provides a standard daily dose of progestogens for 5 years, whereas the oral progestogen treatment is likely to be discontinued by clinicians following the evidence of disease regression: in our cohort this was commonly at 6 months. Despite stopping the progestogen treatment we did not observe any cases of relapse after 48 months. This is in contrast to a few relapse events after discontinuing LNG-IUS treatment at 5 years. We are unable to explain this difference between the oral and LNG-IUS groups but this should highlight to the clinicians that relapse may occur after stopping LNG-IUS treatment after a 5-year period. It is envisaged that if the precipitating cause for EH, such as HRT, ceases to exist during follow-up, it is unlikely that EH will reoccur. In other cases, if the cause is not abolished, as is often the case with obese women, the high estrogen concentrations may be causal to the relapse of EH. Further research should focus on predictors to identify women at high risk of relapse and prioritize their long-term follow-up.

To conclude, this study indicates that relapse for women with ACH or CH treated with progestogens is common. Discontinuing follow-up after an initial regression is not justified and follow-up should be continued for at least 5 years and particularly so after LNG-IUS treatment is stopped. Women who relapse during the follow-up should be subjected to hysterectomy as there may be underlying undiagnosed endometrial cancer.

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Authors' roles

I.D.G. and J.K.G. designed and executed the study. P.K., M.S., R.G. with I.D.G. analyzed the data. I.D.G. drafted all manuscripts and all authors contributed to the critical discussion.

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Conflict of interest

None declared.

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